REMARKS

Claims 23-42 were pending in the present application. Claims 23-42 are rejected and claims 23 and 41 are objected to. By virtue of this response, claims 23, 27-30, 32-34, 39, and 41 have been amended, claim 31 is cancelled, and new claims 43-46 are added. Accordingly, claims 23-30 and 32-46 are currently under consideration. Allowance of the pending claims is respectfully requested.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and, moreover, have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claim Amendments

The amendments to claims 23, 27-30, 32-34, 39, and 41, as well as new claims 43-46, are fully supported by the original application. No new matter is added by the amendments to the claims.

Claims 23 and 41 have been amended to correct typographical errors.

Claim 27 has been amended so that it is an independent claim directed to a pharmaceutical composition for the treatment of a tumor disease in a patient, comprising antigen-presenting cells into which proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells have been introduced, wherein the antigen-presenting cells are HLA-haploidentical with respect to those of the patient. Claim 27, as amended, is no longer a dependent claim. Support for the amendment of claim 27 is found, e.g., in claims 27 and 31 prior to amendment, as well as throughout the application as filed. Dependent claims 28-30 and 32 have been amended due to the amendment of claim 27. Claim 31, which was previously directed to a pharmaceutical composition, has been cancelled.

Claim 33 has been amended so that it is an independent claim directed to a method of treatment of tumor diseases in a patient comprising administering to said patient a therapeutically effective amount of HLA-haploidentical antigen-presenting cells into which proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells have been introduced.

Claims 28, 34, and 39 have all been amended to delete the "preferably" language. New claim 43 finds support in claim 28 prior to amendment. New claim 44 finds support in claim 34 prior to amendment. New claims 45 and 46 find support in claim 39 prior to amendment.

Claim Objections

The Office has objected to claim 41 because there is no space between "HLA" and "haploidentical," and there is a period before "and/or." Since claim 41 has now been amended to correct the typographical errors, Applicants respectfully request that the objection to claim 41 be withdrawn.

The Office has objected to claim 23 because it comprises an extraneous verb: "introducing proteins and/or peptides....are introduced." Since claim 23 has now been amended to correct the typographical error, Applicants respectfully request that the objection to claim 23 be withdrawn.

Claim Rejections under 35 U.S.C. § 112

Claims 28, 34 and 39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 28, 34, and 39 have now been amended to remove the "preferably" language from the clams. Accordingly, Applicants respectfully request that the rejection of claims 28, 34, and 39, under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim 32 is rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

Claim 32, as amended, is directed to a pharmaceutical composition for the treatment of a tumor disease in a patient, comprising antigen-presenting cells into which proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells have been introduced, wherein the antigen-presenting cells are HLA-haploidentical with respect to those of the patient, and wherein the pharmaceutical composition is characterized in that it is a vaccine.

The Office contends that a vaccine must by prophylactic, citing Stedman's Medical Dictionary, 2000. The Office further asserts that the specification allegedly does not provide any teaching of the prophylaxis of cancer, how to determine the individuals who will develop a particular cancer, nor how to effectively prevent said particular cancer type before occurrence. The Office contends that one of skill in the art would not be able to use the composition of the invention as a vaccine without undertaking to determine how to select for individuals which will develop a particular cancer type before the said cancer occurs in the individual. In addition, the Office contends that the prior art was not mature with respect to how to elicit an effective prophylactic memory cell response that would persist in an individual not harboring tumor cells.

Applicants respectfully disagree. The Office's arguments appear to be based on its equation of "vaccine" with "prophylactic vaccine." Such a limited meaning of "vaccine" contradicts the Office's own cited reference, the specification, and the understanding of those skilled in the art.

Applicants respectfully submit that the Office's strong reliance on Stedman's Medical Dictionary in support of its assertion of the meaning of a vaccine is inappropriate. Applicants submit that the citation provided by the Office clearly encompasses a treatment use for a vaccine in its description of "rabies vaccine" on page 2, which states "introduced by Pasteur as a *method of treatment* for the bite of a rabid animal" (see page 2 of excerpt provided to Applicant; emphasis

added). See also entry for "staphylococcus vaccine" which is used for "furunculosis, acne, and other suppurative conditions." Accordingly, Applicants submits that the Patent Office's own reference indicates that vaccines may be employed not just for prophylaxis, but for treatment purposes as well.

Furthermore, the Office must consider the term "vaccine" in light of the specification and from the perspective of one of ordinary skill in the art after having considered the application as a whole. On pages 4-6, of the specification, as well as throughout the specification and original claims, the application clearly discloses the use of the present compositions in the *treatment* of tumors. Thus, even if the Office's dictionary reference teaches that a vaccine *can*, in some instances, be prophylactic, the Office's asserted meaning of "vaccine" is clearly contrary to the meaning intended by the instant specification which clearly encompasses therapeutic treatments.

In addition, Applicants respectfully submit that it was commonly understood in the field of oncology that tumor vaccines were typically designed to treat existing tumors. The Office's attention is directed to U.S. Patent No., 4,415,553 to Zhabilov et al. (filed 1980 and issued 1983), which clearly discloses treating tumors with an anti-tumor vaccine. Additional references that teach antitumor vaccines for treatment purposes include, but are not limited to, U.S. Patent Nos. 4,568,542; 4,789,658; 4,877,611; 5,156,841; 5,290,551; and 5,582,831.

Since Claim 32 is fully enabled, Applicants respectfully request the withdrawal of the rejection of claim 32 under 35 U.S.C. § 112, first paragraph.

Claim Rejections under 35 U.S.C. § 102

Claims 23, 27, 28, 30, 31 and 40 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Greenman et al. (WO 99/03976). Applicants respectfully traverse this rejection.

Claim 23, as amended, is directed to a method for the generation of HLA-haploidentical antigen-presenting cells for the treatment of tumor diseases in a patient. The method comprises providing antigen-presenting cells from a donor which are HLA-haploidentical with respect to those

of the patient and introducing proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells into the HLA-haploidentical antigen-presenting cells. Claim 27, as amended, is directed to a pharmaceutical composition for the treatment of a tumor disease in a patient, comprising antigen-presenting cells into which proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells have been introduced, wherein the antigen-presenting cells are HLA-haploidentical with respect to those of the patient. Claims 28 and 30, as amended, are directed to certain pharmaceutical compositions of claim 27. Claim 31 is cancelled, without prejudice, thereby rendering the rejection moot with respect to this claim. Claim 40 is directed to the method of claim 23 characterized in that the antigen-presenting cells are dendritic cells or macrophages.

To anticipate a claim, a reference must teach or suggest each and every element of the claim. Greenman et al. fails to anticipate claims 23, 27, 28, 30, and 40 because the reference fails to teach or suggest each and every element of the claims. In particular, Greenman et al. does not teach or suggest the production or use of antigen-presenting cells from donors which are HLA-haploidentical as the term "HLA-haploidentical" is used by Applicants in the specification of the present application.

The last full paragraph of page 7 of the specification of the present application states as follows:

> "HLA-haploidentical antigen-presenting cells have class I (HLA-A, -B, and –C) molecules in common with the patient which are encoded by the HLA-A, -B, and –C alleles of one chromosome. They also have class II molecules (HLA-DR, -DQ, and –DP) in common with the patient encoded by the corresponding alleles of the same chromosome."

Accordingly, the HLA-haploidentical antigen-presenting cells of the present application have *each* of the class I molecules HLA-A, -B, and -C *and each* of the class II molecules HLA-DR, -DQ, and -

DP that are encoded by the corresponding alleles of a chromosome in common with those of the patient.

By contrast, Greenman et al., states that allogeneic donor and host are preferably matched in three or more of the six HLA loci corresponding to HLA-A, -B, and -DR and in "'haploidentical' transplantation" are matched in three of the six HLA loci (Greenman et al., page 26, lines 25-27), but is silent with respect to other HLA loci (e.g, HLA-C, HLA-DQ, and HLA-DP), and with respect to whether the matching loci should be on the same chromosome. Greenman et al. further states that the donor and recipient are ideally "identical for HLA-A, B and DRB1" (Greenman et al., page 26, lines 27-28), but again is silent with respect to other HLA loci. Nowhere does Greenman et al. either teach or suggest the production or use of antigen-presenting cells that are *HLA-haploidentical* with respect to those of the patient in the manner indicated on page 7 of the specification of the present application and into which proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells have been introduced.

Since Greenman et al. does not teach or suggest each and every element of claims 23, 27, 28, 30, and 40, Applicants respectfully request that the rejection of claims 23, 27, 28, 30, and 40 under 35 USC § 102(b) be withdrawn.

Claims 23, 27, 28, 30, 31, 33, 34, and 37-40 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Cohen (WO 98/33527). Applicants respectfully traverse this rejection.

Claims 23, 27, 28, 30, and 40 are as indicated above with respect to the rejection under 35 U.S.C. 102(b) over Greenman et al. Claim 31 is cancelled without prejudice, thereby rendering the rejection moot with respect to claim 31. Claim 33, as amended, is directed to a method of treatment of tumor diseases in a patient comprising administering to said patient a therapeutically effective amount of HLA-haploidentical antigen-presenting cells into which proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed

in tumor cells or are derived from autologous tumor cells have been introduced. Claim 34 is directed to certain methods of claim 33. Claim 37 is directed to a method of claim 23 characterized in that the HLA-haploidentical antigen-presenting cells are applied by the intravenous, subcutaneous or intramuscular route. Claim 38 is directed to a method of claim 23 wherein the proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells have been introduced into the HLA-haploidentical antigen-presenting cells in recombinant form. Claim 39 is directed to certain methods of claim 23.

As noted above with respect to the rejection of claims 23, 27, 28, 30, and 40 under 35 U.S.C. 102(b) over Greenman et al., page 7 of the specification of the present application indicates that the HLA-haploidentical antigen-presenting cells have the class I molecules HLA-A, -B, and -C and the class II molecules HLA-DR, -DQ, and -DP that are encoded by the corresponding alleles on one chromosome in common with those of the patient.

By contrast, Cohen more generally describes the use of semi-allogeneic cells, rather than specifically HLA-haploidentical cells, and indicates that in one embodiment, "most alleles coding for the various HLA specificities are unmatched between the antigen-presenting cell and the recipient" (page 23, lines 4-7, of Cohen). Even when Cohen states that the phrase "most alleles being unmatched at the various HLA specificities" refers to unmatched alleles of "from about 50% to less than 100%" (page 23, lines 7-11, of Cohen), Cohen fails to teach or disclose that all of the alleles encoding both the class I molecules HLA-A, -B, and -C and the class II molecules HLA-DR, -DQ, and –DP on the same chromosome are matched. Even if Cohen's "from about 50% to less than 100%" includes an exactly 50% mismatch of alleles, nothing in Cohen teaches or suggests that the 50% matched alleles must include *all* of the alleles encoding both the class I molecules HLA-A, -B, and -C and the class II molecules HLA-DR, -DQ, and –DP on the *same* chromosome, and numerous possible combinations of 50% matched and 50% unmatched alleles would exist since an antigen-presenting cell contains two alleles encoding each MHC molecule, one on each haplotype. For instance, a 50% match could indicate that the alleles on both haplotypes that encode 50% of the MHC molecules are identical to the intended recipient, but that the alleles on both haplotypes that

encode the other 50% of the MHC molecules differ from the intended recipient. Thus, in many instances, the cells having the characteristics described in Cohen would clearly not be HLA-haploidentical to the intended recipient.

Since Cohen does not teach or suggest each and every element of claims 23, 27, 28, 30, 33, 34, and 37-40, Applicants respectfully request that the rejection of claims 23, 27, 28, 30, 33, 34, and 37-40 under 35 USC § 102(b) be withdrawn.

Claims 27-31 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Kugler et al. Applicants respectfully traverse this rejection.

As noted above, claim 27, as amended, is directed to a pharmaceutical composition for the treatment of a tumor disease in a patient, comprising antigen-presenting cells into which proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells have been introduced, wherein the antigen-presenting cells are HLA-haploidentical with respect to those of the patient. Claims 28-30, as amended, are directed to certain pharmaceutical compositions of claim 27. Claim 31 is cancelled, without prejudice, thereby rendering the rejection moot with respect to this claim.

To anticipate a claim, a prior art reference must teach or suggest each and every limitation of the claim. Kruger et al. does not anticipate claims 27-30, as amended, because Kruger et al. does not teach or suggest each and every limitation of claims 27-30.

Kugler et al. describes hybrids formed between allogeneic dendritic cells (DCs) derived from an unrelated donor and autologous tumor cells from a patient. Nowhere, however, does Kugler et al. teach or suggest the use of cells that are HLA-haploidentical with respect to the patient to be treated. If a patient having two HLA haplotypes **a** and **b** is treated by the method reported in Kugler et al., then one or more allogeneic dendritic cells having, e.g., two HLA haplotypes **c** and **d**, would be fused with tumor cells from the patient (i.e., cells having the two HLA haplotypes **a** and **b**). If all chromosomes from the fused cells were maintained in the resulting hybrid cells (Kugler et al. is silent on this point), the resulting hybrid cells would be expected to contain the two HLA-

haplotypes **a** and **b** (from the autologous tumor cell) as well as the two HLA-haplotypes **c** and **d** (from the allogeneic dendritic cells). A cell containing two HLA haplotypes **a** and **b** that are syngeneic to the patient and two HLA haplotypes **c** and **d** that are allogeneic to the patient is *not* a cell that is HLA-haploidentical with respect to the patient to be treated with the composition.

Finally, Applicants note that Kruger et al. has been unanimously retracted by the authors "because of several incorrect statements and erroneous presentation of the primary data, results and conclusions." *See* Nature Medicine 2003 Sept; 9(9):1221, a copy of which is included in the Information Disclosure Statement filed herewith. This retraction calls into question whether the teachings of Kruger et al. are enabled. Following the retraction, those in the art would be unlikely to rely upon the reference.

Since Kugler et al. does not teach or suggest each and every element of claims 27-30, as amended, Applicants respectfully request that the rejection of claims 27-30 under 35 USC § 102(b) be withdrawn.

Claim Rejections under 35 U.S.C. § 103

Claims 23, 26-28, 30, 31, 33-35 and 37-40 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Cohen, in view of Kugler et al. Applicants respectfully traverse this rejection.

Claims 23, 27-28, 30, 33-34 and 37-40 are as described above. Claim 26 is directed to a method of claim 23, wherein antigen-presenting cells of two different HLA-haploidentical individuals are used. Similarly, claim 35 is directed to a method of claim 33 characterized in that HLA-haploidentical antigen-presenting cells of two different HLA-haploidentical individuals are used. Since claim 31 is cancelled, the rejection is moot with respect to this claim.

To establish a prima facie case of obviousness, the prior art reference must teach or suggest all claim limitations. Applicant respectfully submits that the combination of Cohen and Kugler et al. does not teach or suggest all elements of the claims. As discussed above with respect

to the rejections under 35 U.S.C. §102 over Cohen or Kugler et al., neither Cohen nor Kugler et al. teaches or suggests the production or use of *HLA-haploidentical* antigen presenting cells into which proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells are introduced for the treatment of tumor disease in a patient.

Since Cohen et al. in view of Kugler et al., does not teach or suggest each and every element of claims 23, 26-28, 30, 33-35 and 37-40, Applicants respectfully request that the rejection of claims 23, 26-28, 30, 33-35 and 37-40, under 35 U.S.C. §103(a) be withdrawn.

Claims 23, 25-28, 30, 31, and 33-40 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Cohen and Kugler et al., and further in view of Eastman et al. (WO 01/36680) and Schuller et al. (WO 02/36790). This rejection is respectfully traversed.

Claims 23, 26-28, 30, and 33-35 and 37-40 are as described above. Claim 25 is directed to the method of claim 23 characterized in that first RNA from tumor cells is reverse transcribed into cDNA, the cDNA is amplified by means of PCR and subsequently the cDNA is transcribed into RNA. Claim 36 is directed to the method of claim 35 characterized in that RNA is employed which has been reverse transcribed from autologous tumor cells into cDNA, the cDNA has been amplified by means of PCR and subsequently the cDNA has been transcribed into RNA. Since claim 31 is cancelled, the rejection is moot with respect to this claim.

As previously noted, to establish a prima facie case of obviousness, the prior art reference must teach or suggest all claim limitations. Applicant respectfully submits that the combination of Cohen and Kugler et al., further in view of Eastman et al. and Schuller et al., does not teach or suggest all elements of the claims. None of the cited references, either alone or in combination, teaches or suggests the production or use of *HLA-haploidentical* antigen presenting cells into which proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived from autologous tumor cells are introduced for the treatment of tumor disease in a patient. Further explanation of the failure of

Cohen and Kugler et al. to teach or suggest the required elements is provided above in response to the rejections under 35 U.S.C. §102 over Cohen and Kugler et al., individually.

Since Cohen et al. in view of Kugler et al., in view of Eastman et al. and Schuller et al., does not teach or suggest each and every element of claims 23, 25-28, 30, and 33-40, Applicants respectfully request that the rejection of claims 23, 25-28, 30, and 33-40, under 35 U.S.C. §103(a) be withdrawn.

Claims 23-31 and 33-42 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Cohen, Kugler, Eastman and Schuller et al., and further in view of Warnier et al. (WO 98/58956). This rejection is respectfully traversed.

Claims 23, 25-28, 30, 33-40 are as described above. Claim 24 is directed to the method of claim 23, wherein proteins and/or peptides or RNA or DNA or cDNA, respectively, encoding said proteins and/or peptides from several different tumor cell lines are introduced into the HLA-haploidentical antigen-presenting cells. Claim 29 is directed to the pharmaceutical composition of claim 27, wherein the HLA-haploidentical antigen-presenting cells contain proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides from several different tumor cell lines. Claim 41 is directed to the method of claim 23, wherein, into the HLA-haploidentical antigen-presenting cells, proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides from several different tumor cell lines have been introduced for the treatment of tumor diseases in said patient. Claim 42 is directed to the method according to claim 41 wherein pooled cRNA from two or three different tumor cell lines is introduced. Since claim 31 is cancelled, the rejection is moot with respect to this claim.

Applicant respectfully submits that the combination of Cohen and Kugler et al., Eastman et al., Schuller et al., and Warnier et al. does not teach or suggest all elements of the claims. None of the cited references, either alone or in combination, teaches or suggests the production or use of *HLA-haploidentical* antigen presenting cells into which proteins and/or peptides or RNA or DNA or cDNA encoding said proteins and/or peptides which are overexpressed in tumor cells or are derived

from autologous tumor cells are introduced for the treatment of tumor disease in a patient. Further explanation of the failure of Cohen and Kugler et al. to teach or suggest the required elements is provided above in response to the rejections under 35 U.S.C. §102 over Cohen and Kugler et al., individually.

Since the combination of Cohen et al., Kugler et al., Eastman et al., Schuller et al., and Warnier et al. does not teach or suggest each and every element of claims 23-30 and 33-42, Applicants respectfully request that the rejection of claims 23-30 and 33-42, under 35 U.S.C. §103(a) be withdrawn.

Double Patenting

Claims 23-42 are provisionally rejected under 35 U.S.C. § 101 as allegedly claiming the same invention as that of claims 1-20 of copending Application No. 10/665,421. In responding to this rejection, Applicants assume that the Office intended this provisional rejection to reference Application No. 10/663,421, the parent application of the present application, not Application No. 10/665,421, since Application No. 10/665,421 is unrelated to the present application. If this assumption is not correct, clarification on the record is requested. Applicant respectfully traverses this provisional rejection.

Applicants submit that Application No. 10/663,421 is no longer pending and has been abandoned. In the absence of allowed conflicting claims in Application No. 10/663,421, Applicants respectfully request withdrawal of the provisional rejection of claims 23-42 under 35 U.S.C. § 101.

Information Disclosure Statement filed April 26, 2004

An Information Disclosure Statement and Form PTO-1449 were filed on April 26, 2004. A copy of the initialed Form PTO-1449 was not included with the Non-Final Office Action mailed June 28, 2006. Therefore, we respectfully request the Examiner to provide us with a copy of the initialed Form PTO-1449 for the Information Disclosure Statement filed on April 26, 2004.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 559412000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 28, 2006

Respectfully submitted,

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